REMARKS

Claims 1-14, 16-33, 35-41, 43-68, 70-87, 89-95, and 97-108 are under examination. With this Reply and Amendment, Claims 1, 4, 11, 16, 19, 20, 27, 55, 58, 65, 70, and 73 have been amended, Claims 5, 6, 7, 28-54, 59-61, 82-108 have been canceled without prejudice, and claims 109 and 110 are newly added. Support for the amendments and new claims is found in the specification and claims as originally filed. Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications. Applicant's acknowledge the withdrawal of the election of species requirement. Reconsideration of the claims in light of the following remarks is requested.

CLAIM OBJECTIONS

Claim Objections

Claims 4, 31, 58, and 85 were objected to for a capitalized "Calcium."

Claims 11, 38, 65, and 92 were objected to for having typographical errors in the words "R_1AR, ~3_2AR, R1AR, f32AR, ~3_1AR_1, ~3_2AR_1, ~31AR."

Claim 19 was objected to as having a missing claim number.

Claim 27 was objected to as having a typographical error in the phrase "dose response curse."

Claim 73 was objected to as having a typographical error in the phrase "the est compound."

The rejection is moot with respect to canceled Claims 31, 38, 85, 86 and 92. Claims 4, 11, 19, 27, 58, 65, and 73 have been amended to correct informalities. Withdrawal of the objections is respectfully requested.

CLAIM REJECTIONS AND RESPONSES

Claim Rejection Under 35 U.S.C. § 112 (first paragraph)

Claims 1-14, 16-33, 35-41, 43-68, 70-87, 89-95, and 97-108 are rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification, while being enabling for a method of identifying a transmembrane receptor (TMR) agonist wherein the cell such as U2OS cell line expresses an arrestin-GFP conjugate, does not reasonably provide enablement for a method of identifying a transmembrane receptor (TMR) agonist wherein the cell has biologically active fragment of a TMR or where the cell further comprises biologically active fragments of arrestin. The Examiner further states that Applicant is not enabled for modifying the agonists or ligand. Applicants respectfully traverse.

A. The Legal Standard

Under 35 U.S.C. §112 (first paragraph), a patent specification containing a teaching of how to make and use the invention must be taken as enabling unless the PTO provides sufficient reason to doubt the accuracy of the disclosure. *In re* Marzocchi, 439 F.2d 220, 223-224, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). The claimed invention as disclosed in the specification cannot be questioned on the unsupported skepticism of the Examiner. *Ex parte* Linn, 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte* Rosenwald, 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959). The number and variety of examples is irrelevant if the disclosure is "enabling" and set forth the "best mode contemplated." Even in an unpredictable art, Section 112 does not require disclosure of a test of every species encompassed by the claims. *In re* Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

In addition, an invention is enabled even though the disclosure may require some routine experimentation to practice the invention. Hybritech v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. ML T v. A.B.

Fortia, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re* Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); In re Jackson, 217 U.S.P.Q. 804, 807 (PTO Pt. Bd. App. Int. 1982). Finally, the Examiner has the burden of showing that the disclosure entails undue experimentation. *In re* Angstadt, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976).

B. Meeting the Legal Standard

The Examiner's grounds for lack of enablement are focused on assertions that specification does not reasonably provide enablement for a method of identifying a transmembrane receptor agonist wherein the cell has a biologically active fragment of a TMR, where the cell further comprises biologically active fragments of arrestin. The Examiner further states the specification is not enabling for "modifying" the agonists or ligand. Applicants respectfully traverse the enablement rejections and submit that the specification provides written description support and enables a method for identifying transmembrane receptor (TMR) agonists.

The Examiner cites a number of references in the art to support the conclusion that the state of the art is unpredictable. Specifically, the Examiner cites Ghosh, *et al.* J. Biomol. Screening 10(5):476-484 (2005) and Vassilatis, et al. (PNAS 100 (8):4903-4908, 2003) for the proposition that variability in structure, characteristics and functions of the superfamily of GPCRs between species such as mouse, pig, primate and human is great and alleges that there is insufficient guidance or working examples for a claims of identifying any TMR agonists from human, mouse, pig and primate.

Applicants respectfully submit that the specification provides written description support and enables a method for identifying transmembrane receptor (TMR) agonists across multiple species. The assay, in part, is a universal assay that is independent of variability in the structure, characteristics and functions of the TMRs.

As described in the specification, the "cellular mechanism mediating initial steps of agonist-specific internalization is a two-step process in which agonist-occupied receptors are phosphorylated by a kinase, for example a GPCR kinase (GRK), and then bind an arrestin protein. TMRs, of which GPCRs are but one example, may bind an arrestin protein, and subsequently be internalized. The type III TGF-beta receptor is an example of a TMR, other than a GPCR, that binds arrestin, and undergoes subsequent internalization and signaling down-regulation (Chen *et al.*, 2003, Science 301:1394-1397)." Specification at Paragraph 11, emphasis added.

In addition, the cited art Ghosh, *et al* supports the universal assay as presently claimed. "Cytoplasmic proteins, termed arrestin, rapidly translocate to and bind the activated receptor at the plasma membrane and sterically uncouple the receptor from its cognate G-protein, thereby attenuating the signaling events. This process, common to nearly all GPCR, is determined desensitization. Arrestin also mediate the internalization of the activated receptors by targeting them to clathrin coated pits and may also play a role in the extent to which the receptors recycle back to the plasma membrane (resentization) or are degraded in lysosomes (down regulated).

Finally, as discussed below, the specification teaches hundreds of TMRs from several species, including human and rat. Further the specification discloses experiments with rat and human GPCR (Example 1) and identifying morphine as an opiod agonist.

Applicants respectfully submit that the specification further provides written description support and enables a method for identifying transmembrane receptor (TMR) agonists with "biologically active" fragment a TMR and "biologically active" fragment of an arrestin. As described in the specification, a TMR "can activate intracellular signaling". Specification at paragraph 007. Therefore it would be apparent to one skilled in the art that a biologically active fragment of a TMR can activate intracellular signaling. Likewise the biological activity of an arrestin is know in the art and clearly described in the specification. As described in the speciation at paragraph 0011 an arrestin binds activated receptor.

Therefore it would be apparent to one skilled in the art that a biologically active fragment of an arrestin can bind an activated receptor.

As such, both the working examples and specification provide an extensive discussion of method for identifying transmembrane receptor (TMR) agonists. Accordingly, Applicants respectfully submit that the specification fully enables the present claims, and respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Claims 1-14, 16-33, 35-41, 43-68, 70-87, 89-95, and 97-108 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse.

The written description requirement is satisfied if the specification clearly conveys to those skilled in the art, that the applicant was in possession of the invention defined by the current claims, as of the filing date. *Vas-Cath, Inc. v. Mahurkar* 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Every nuance of the claims need not be explicitly described in the specification to satisfy the written description requirement of 35 U.S.C. § 112. *Vas-Cath* 19 USPQ2d at 1116. Thus, procedures or terms, which are conventional or well known to those of skill in the art, need not be disclosed in detail. *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81, 94 (Fed. Cir. 1988). Claims drawn to the use of chemical compounds in a manner auxiliary to the invention need have a written description only as specific as necessary to direct one having ordinary skill in the art to that class of compounds. *In re Herschler* 200 USPQ 711 (CCPA 1979). Functional recitation of compounds in the specification can provide such that description. *Herschler* 200 USPQ 711.

The Examiner states at Page 9 that there are two species of the claimed genera disclosed that is within the claimed genera *i.e.* a μ opiod receptor representing the genus of TMR and arrestin-GFP respecting arrestin genus. Applicants respectfully disagree and direct the Examiner to the below cited sections of the specification.

TMR or transmembrane receptors are proteins that span membranes and have the ability to interact with or bind a ligand. The magnitude of the physiological responses controlled by TMRs can be linked to the balance between TMR signaling and signal termination. The signaling of GPCRs and some other TMRs is controlled by a family of intracellular proteins called arrestins. Specification at paragraph 004. The specification disclose several arrestins, including but not limited to visual arrestin (sometimes referred to as Arrestin 1), cone arrestin (sometimes referred to as arrestin-4), ß-arrestin 1 (sometimes referred to as Arrestin 2), and ß-arrestin 2 (sometimes referred to as Arrestin 3). Specification at Paragraphs 29 and 120.

In addition, Applicants have provided hundreds of GPCRs that can be used in the invention, as well hundreds GPCR agonists or ligands useful in the present invention. See for example FIGS. 1, 2 and 3.

Accordingly, the Specification describes species sufficiently to guide those of ordinary skill in the art. In addition, Applicants have shown, *supra*, that desensitization by arrestin and receptor internalization are common features common to the members of the genus.

Therefore, the pending Claims are in compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. In view of the foregoing, Applicants respectfully request that the rejections, *supra*, of Claims 31-55 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejection Under 35 U.S.C. § 112 (second paragraph)

Claims 1-14, 16-33, 35-41, 43-68, 70-87, 89-95, and 97-108 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 28, 55 and 82 stand rejected as omitting the essential step of correlation. The rejection is moot with respect to canceled Claims 28 and 82. Claims 1 and 55 have been amended to clarify the correlation step of "wherein reduced TMR internalization indicates a TMR agonist".

Claims 1, 28, 55 and 82 stand rejected as the phrase "biologically active" is allegedly indefinite. Specifically the Examiner states that the phrase "biologically active", is indefinite because the specification allegedly does not define the biological activity of the fragments. The rejection is moot with respect to canceled Claims 28 and 82, and traversed with respect to Claims 1 and 55. As described in the specification, a TMR "can activate intracellular signaling". Specification at paragraph 007. Therefore it would be apparent to one skilled in the art that a biologically active fragment of a TMR can activate intracellular signaling. Likewise the biological activity of an arrestin is know in the art and clearly described in the specification. As described in the speciation at paragraph 0011 an arrestin binds activated receptor. Therefore it would be apparent to one skilled in the art that a biologically active fragment of an arrestin can bind an activated receptor.

Claims 6, 28, 60 and 82 stand rejected as the phrase "modified" is allegedly indefinite. Applicants respectfully traverse the rejection. However, in order facilitate prosecution of the application, Applicants have canceled claims 6, 28, 60 and 82

Claims 7, 33, 61 and 87 stand rejected as the phrase "pharmaceutically relevant compounds" is allegedly indefinite. Applicants respectfully traverse the rejection. However, in order facilitate prosecution of the application, Applicants have canceled claims 7, 33, 61 and 87.

Claim 4 stands rejected as phrase "may be" is allegedly indefinite. Applicants have amended Claim 4 to replace "maybe" with "is".

Claim 20 stands rejected as phrase "approximately equal" is allegedly indefinite. Applicants have amended Claim 20 to delete the term "approximately".

Claims 16, 43, 70 and 97 stand rejected as allegedly indefinite for recitation of a broad limitation in the same claims as a narrow limitation. The rejection is moot with respect to canceled Claims 43 and 97. Applicants have amended Claim 16 and 70 delete the term human, and have added new claim 109 and 110 directed to a human TMR.

Claim Rejection Under 35 U.S.C. § 102

Claims 1-3, 5, 9, 11-13, 16, 20, 55-59, 63-67, 70, and 74 are allegedly rejected under 35 U.S.C. § 102(b) as being anticipated by Barak *et al.* (US Patent 6,110,693). The rejection is moot with respect to canceled Claims 5 and traversed with respect to pending Claim 1 and 55 and the dependent Claims.

"A claim is anticipated only if *each and every element* as set forth in the claim is found, either expressly or inherently described, *in a single prior art reference*." *Verdegaal Bros. v. Union Oil Co. of California* 2 USPQ2d 1051, 1053 (Fed. Cir. 1987), emphasis added. See also, MPEP § 2131.

Barak *et al.* is directed in part a methods of screening a test compound for G protein coupled receptor (GPCR) agonist activity, with a cell expressing a GPCR and an arrestin detectable molecule conjugate, exposing the cell to a test compound, and detecting movement of the detectable molecule to the membrane edge after exposure of the cell to the test compound.

Independent Claims 1 and 55, recite in part, methods of identifying a transmembrane receptor (TMR) agonist, wherein the TMR agonist (TMRA) is capable of activating TMR signaling while exhibiting reduced TMR internalization over a control compound, comprising the steps of (a) through (d) and

(e) quantitatively determining if the TMR internalization is reduced by comparing the TMR internalization in the presence of the test compound to the TMR internalization in the presence of a control compound, and wherein the signaling is activated as compared to TMR signaling in the absence of agonist; and

(f) wherein reduced TMR internalization identifies a TMR agonist.

Barak *et al.* fails to teach, *inter alia*, quantitatively determining if the TMR internalization is reduced by comparing the TMR internalization in the presence of the test compound to the TMR internalization in the presence of a control compound, and wherein the signaling is activated as compared

to TMR signaling in the absence of agonist; and wherein reduced TMR internalization indicates a TMR agonist which is a required element of Claims 1 and 55. Accordingly, Barak *et al.* fails to anticipate independent Claims 1 and 55. Claims 2, 3, 5, 9, 11-13, 16, 20 ultimately depend from Claim 1 and Claims 56-58, 63-67, 70, and 74 ultimately depend from Claim 55 are therefore likewise not anticipated by Barak *et al.* In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102 (b) over Barak *et al.* be withdrawn.

Claim Rejection Under 35 U.S.C. §103

Claims 1, 4, 7, 10, 19, 31-33, 37, 46, 58, 64, 73, 82, 85-87, and 91 are allegedly rejected under 35 U.S.C. § 103(a) as being unpatentable over Barak *et al.* (U.S. Patent 6,110,693). The rejection is moot with respect to canceled Claims 7, 31-33, 37, 46, 82, 85-87, and 91 and is traversed insofar as it pertains to presently pending independent Claims 1 and 55 and their dependent Claims on the grounds that the Patent Office has filed to establish a *prima facie* case of obviousness.

The Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell* 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Patent Office to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. The motivation to modify and/or combine references and the reasonable expectation of success, must come from the prior art, not Applicants' disclosure. *In re Vaeck* 20 USPQ2d 1438 (Fed. Cir. 1991).

According to the Patent Office, Barak *et al.* teach a method of assessing GPCR pathway activity under test conditions, by providing a test cell that expresses a GPCR and that contains a conjugate of a β-arrestin protein and a detectable molecule; exposing the test cell to a known GPCR agonist under test

conditions; and then detecting translocations of the detectable molecule from the cytosol of the test cell to the membrane edge of the test cell.

Knudsen, *et al.* (WO0246763) teaches that activation of GPCR may be determined by measuring the level of cAMP, Ca^{2+}, or via the ^{35}S-GTPgammaS assay and that chemical libraries, such as combinatorial chemical libraries, comprise chemical compounds that have been synthesized from a synthetic series of reactions. The Patent Office, from the above, concludes that it would have been *prima facie* obvious to one of ordinary skill in the art to combine use the method of Barak *et al.* to test compounds from combinatorial libraries taught by Knudsen *et al.*, as presently claimed. Applicants respectfully disagree.

As described above, Barak *et al.* fails to teach every element of the claimed methods. The secondary reference, Knudsen *et al* , does not cure the deficiencies of Barak *et al.* None of the cited references, individually or in combination, teach or suggests the instant invention. Because Barak *et al.* and Knudsen *et al*, alone or in combination, fail to teach or suggest each and every limitation of the claimed invention, the Examiner has failed to establish a *prima facie* case, and the obviousness rejection should be withdrawn. Accordingly, the inventions recited in independent Claims 1 and 55 are unobvious over the disclosures of Barak *et al and* Knudsen *et al.* The claims dependent on Claims 1 and 55 are patentable for at least the same reasons. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) as it pertains to pending independent Claims 1 and 55 and the dependent Claims be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,
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